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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/088,724 | 06/14/2002 | Ikuo Nishimoto | 082377-00000US | 6929 |

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| EXAMINER | |
|---|---|
| CHERNYSHEV, OLGA N | |
| **ART UNIT** | **PAPER NUMBER** |
| 1649 | |

DATE MAILED: 11/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/088,724 | NISHIMOTO, IKUO | |
| | Examiner | Art Unit | |
| | Olga N. Chernyshev | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-8,13,15,16,20-22,27-30,35-38,43 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,21 and 22* is/are allowed.

6)☒ Claim(s) *2,4-8,13,15,16,20,27-30,35-38,43 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 14, 2005 has been entered.

### *Formal matters*

2. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

### *Response to Amendment*

3. Claims 2, 5, 6, 13, 15, 16, 20, 28-30, 36 and 45 have been amended and claims 23-26, 31-34, 39-42 and 44 have been canceled as requested in the amendment filed on October 14, 2005. Following the amendment, claims 1, 2, 4-8, 13, 15, 16, 20-22, 27-30, 35-38, 43 and 45 are pending in the instant application.

Claims 1, 2, 4-8, 13, 15, 16, 20-22, 27-30, 35-38, 43 and 45 are under examination in the instant office action.

4. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

6. Applicant's arguments filed on October 14, 2005 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

***Claim Rejections - 35 USC § 112***

7. Claim 2, 4-8, 13, 15 and 16, as amended, stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide that suppresses neuronal death associated with Alzheimer's disease having amino aid sequence of SEQ ID NO: 5 to [...] 60, wherein one amino acid has been substituted, deleted, inserted or added (emphasis added), does not reasonably provide enablement for the full scope of a polypeptide as claimed in section b) essentially for reasons of record in section 8 of Paper mailed on March 16, 2004 and in section 11 of Paper mailed on April 13, 2005. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 2, 5, 6, and dependent claims 4, 7, 8, 13, 15 and 16, as amended, are directed to polypeptides that have amino acid structure such as one amino acid within the sequence has been substituted, deleted, inserted and added to the amino acid sequence defined as SEQ ID NO: 5 to [...] 60, emphasis added. One skilled in the art readily appreciates that this limitation allows for four amino acids to be changed within a generic amino acid sequence of SEQ ID NO: 63 (Formula I, see base claim 1). However, amino acid of SEQ ID NO: 63 has a motif of three amino acids that appear to define the function of the instant polypeptides ("Leu-Thr-(Gly/Ser)").

The instant specification only provides the guidance on how to make and use polypeptide with one amino acid change within the disclosed sequence, wherein the polypeptide suppresses neuronal death associated with Alzheimer's disease. It would require a substantial amount of undue experimentation on part of a skilled artisan to discover how to produce a polypeptide by changing four amino acids within the polypeptide of SEQ ID NO: 63 and retain the activity of the instant polypeptide.

8. Claims 15 and 16 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record in section 10 of Paper mailed on March 16, 21004 and in section 13 of Paper mailed on April 13, 2005. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Beginning at page 14 of the Response, Applicant refers to case law *Cross v. Izuka* and argues that "[t]he specification establishes a correlation between the in vitro and in vivo activity of the claimed polypeptides". Applicant submits that the specification teaches that the claimed polypeptides produced neuroprotective effect for primary neuronal cultures exposed to Aβ *in vitro*, which was selective (page 15) and further refers to publications published after the filing date of the instant specification, which provide additional data that the claimed polypeptide(s) had similar neuroprotective action. Applicant's arguments have been fully considered but are not persuasive for the following reasons.

Claims 15 and 16 are directed to pharmaceutical compositions comprising polypeptide of SEQ ID NO: 63 in the amount effective to prevent or treat neurodegenerative diseases. With

regards to claim breadth, the instant composition, as presented, is claimed to be suitable to prevent and treat any neurodegenerative pathological condition, including neurodegeneration not associated with amyloid pathology. One skilled in the art readily appreciates plurality of factors involved in etiology of neurodegenerative pathology (see review articles by Hardy et al., 1998, Science, 282, pp.1075-9; Offen et al., 2000, J Neural Transm, 58, pp.153-66). The instant specification, as filed provides no guidance, scientific reasoning or factual support that limited information on neuroprotective action of polypeptide of SEQ ID NO: 63 could be extrapolated to prevent and treat any neurodegenerative condition with reasonable expectation of success.

Further, it is well established in the art that because the etiology of Alzheimer's disease is currently not known, no prophylactic measures to prevent the disease are currently available (see Vickers, 2002, Drugs Aging, 19 (7), pp.487-494). The instant specification fails to disclose any factual evidence or rely to information in prior art to support a conclusion that the instant polypeptide of SEQ ID NO: 63 is effective to prevent neurodegeneration or development of Alzheimer's disease. It would require substantial amount of undue experimentation and making significant inventive contribution for one skilled in the art to be able practice the full scope of the claimed invention, as currently presented.

At pages 16-21 of the Response, Applicant presents reasoning that the instant specification is fully enabled for the full scope of using the claimed polypeptides in a pharmaceutical composition to prevent and treat neurodegeneration. Applicant's arguments have been carefully considered but are not persuasive because the art clearly teaches that neurodegeneration in general and Alzheimer's disease in particular are not limited to amyloid pathology. To clarify the Examiner's position, there is no requirement for Applicant to perform

clinical trials to demonstrate enablement (bottom at page 17 of the Response), or to demonstrate that composition comprising the instant polypeptide reverses every possible pathological aspect of Alzheimer's disease (middle at page 18). The standard of enabling disclosure is to be able to practice the instant invention commensurate with its scope with reasonable expectation of success. The Examiner maintains the position that in view of the art recognition of complexity factors involved in the process of neurodegeneration and absence of evidence presented in the instant specification as filed as to how to extrapolate the limited information on beneficial effects of the polypeptide of SEQ ID NO: 63 on experimental survival of neuronal cells to means of prevention and treatment of neurodegeneration, as broadly claimed, the instant specification clearly lacks enablement for the pharmaceutical composition as claimed in claims 15-16.

Therefore, for reasons fully explained earlier and reasons above, the instant rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2, 4, 5-8, 13, 15-16, 20, 27-30, 35-38, 43 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 2, 5 and 6 are vague and indefinite in section b), which recites a polypeptide defined by amino acid sequence (SEQ ID NOs: 5 to 60), wherein such polypeptide contains amino acid substitutions, deletions, insertions and additions, which makes the structure of the claimed molecular embodiments mutually exclusive. Applicant is advised that recitation of "a

polypeptide, which differs from a polypeptide of SEQ ID NO: 5 to [...] 60 in such way that one amino acid has been substituted [...]" might better express the claimed subject matter and obviate this ground of rejection.

11. Claim 5, as amended, is further indefinite for recitation "a mutant sequence of SEQ ID NO: 4". It appears that nucleic acid sequence of SEQ ID NO: 4 is not "a mutant sequence", it is a "cDNA that encodes Humanin, described in SEQ ID NO: 4" (page 16, line 17 of the instant specification). Also, due to the presence of this limitation, the structure of the polynucleotide, as currently claimed, cannot be determined. Clarification is required.

12. Claims 20, 28 and 36 are vague and ambiguous for recitation "amino acid sequence consisting of 3 to 5 arbitrary amino acids (SEQ ID NO: 100)". The metes and bounds of the recitation cannot be determined from the claim or the instant specification because it is not clear how a polypeptide sequence can be consisting of 3 to 5 arbitrary amino acids and at the same time defined by SEQ ID NO: related to a specific ten amino acid sequence. Clarification is required.

13. Claims 4, 7-8, 13, 15-16, 27, 29-30, 35, 37-38, 43 and 45 are indefinite for being dependent from indefinite claims.

***Conclusion***

14. Claims 1, 21 and 22 are allowed. Claims 2, 4-8, 13, 15, 16, 20, 27-30, 35-38, 43 and 45 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.
Primary Examiner
Art Unit 1649

November 1, 2005